REMARKS:

The preceding claim amendments and the following remarks are submitted as a full and complete response to the Office Action issued on October 16, 2009. Claim 1 has been amended to incorporate the subject matter of claim 2, and accordingly claim 2 has been cancelled. Support for the claim amendment can be also found throughout the specification, for example, at paragraphs [0017] and [0018]. No new matter has been added. Upon entry of the claim amendments, claims 1 and 3-5 are pending. Reconsideration of all outstanding rejections is respectfully requested in view of the foregoing amendment and following remarks.

Rejection of Claims 1-5 under 35 U.S.C. §103(a)

The Patent Office has rejected claims 1-5 under 35 U.S.C. §103(a) as being obvious over Carter et al. (US 4,483,849) ("Carter"), Revel et al. (US 4,808,523) ("Revel") and Viscomi et al. (US 5,244,655) ("Viscomi").

Claim 1 is directed to a process for purifying human interferon beta from a recombinant human interferon beta-containing culture comprising performing affinity chromatography and cation exchange chromatography, wherein the affinity chromatography comprises:

adsorbing the interferon beta-containing culture to an equilibrated affinity chromatography column, followed by washing with an equilibration buffer solution;

washing the column with a washing buffer solution A of pH 6.5-7.5 containing 30-60 wt % of propylene glycol;

washing the column with a washing buffer solution C of pH 6.5-7.5 containing 1-

2M NaCl;

washing the column with a washing buffer solution B of pH 6.5-7.5 containing 10-30 wt % of propylene glycol and 1-2M NaCl; and

eluting a human interferon beta-containing fraction with a buffer solution of pH 6.5-7.5 containing 40-60 wt % of propylene glycol and 1-2M NaCl.

Thus, the claimed invention of claim 1 includes three separate washing steps, that is, washing with a washing buffer A, washing with a washing buffer solution B and washing with a washing buffer solution C. However, none of the cited prior art references, either alone or in combination, teaches or suggests the claimed invention.

(1) Disclosure of Carter

Carter discloses a process for purifying and stabilizing interferon, comprising the steps of:

adding an interferon-containing fluid to a solid purification matrix;

eluting said interferon from said matrix with a solution containing propylene glycol; and

storing said interferon in a solution containing propylene glycol (claim 1).

Carter also discloses loading interferon to a column equilibrated with a 1 M NaCl/PO4 buffer (E1), ***washing*** with 40% propylene glycol in the 1 M NaCl/PO4 buffer (E3) and ***eluting*** with 50% propylene glycol (Example 1, second paragraph). Specifically, Carter states that "propylene glycol is more desirable than ethylene glycol in ***eluting*** interferon from Affi-Gel Blue" (column 2, lines 30-32 (emphasis added)) and that "...aqueous solutions of 50% propylene glycol have the unique property of

stabilizing interferon some 10-fold more than the same solutions lacking propylene glycol" (column 2, lines 41-45).

(2) Disclosure of Revel

Revel discloses ***eluting*** recombinant interferon β1 from a Blue-Sepharose column with 20mM phosphate buffer pH 7 containing 1M NaCl, and 40% propylene glycol (PG), ultrafiltrating by using a YM10 membrane and concentrating the filtrate, and further purifying the interferon β1 from the concentrated solution by a column of anti-IFN monoclonal antibody (column 13, line 66-column 14, line 8). However, Revel discloses neither the three separate washing steps using the washing buffer solutions A, B and C, respectively, nor the washing buffer solutions A, B and C.

(3) Disclosure of Viscomi

Viscomi discloses that cation exchange chromatography can be used in the purification of interferon. However, it discloses neither the three washing steps using the washing buffers A, B and C, respectively, nor the washing buffers A, B and C.

(4) Arguments

The claimed method includes the three washing steps including washing with the washing buffer solutions A, B and C, respectively. According to the method, interferon beta can be purified to a high purity of 99% (see paragraph 0046). This can be achieved because each of the three washing steps removes specific kinds of impurities. That is, the washing with the washing buffer A effectively removes impurities with hydrophobicity, the washing with the washing buffer C removes hydrophilic impurities and the washing with the washing buffer B removes impurity proteins (see paragraph 0027 of the specification and FIGS. 3A-3D of the enclosed Experimental Results). In

the absence of solution A, the purity of interferon beta remarkably decreases (see paragraph 0041).

Carter discloses neither the three separate washing steps using washing buffer solutions A, B and C, respectively, nor washing buffer solutions A, B and C. Instead, Carter effectively teaches away from the claimed invention since it discloses a solution containing propylene glycol as an eluting solution. Particularly, it discloses using *50% propylene glycol,* which corresponds to the washing buffer solution A of the claimed invention, as an eluting solution.

The elution is a process of removing adsorbed *interferon* on the affinity chromatography column into the elution solution, while the washing is a process of removing *impurities* including adsorbed proteins *other than interferon* on the affinity chromatography column into the washing solution. Therefore, a person of ordinary skill in the art would not have been motivated to use *50% propylene glycol* as a washing solution because a person of ordinary skill in the art would have expected that if it were used as a washing solution, the interferon on the affinity chromatography column would be removed into the washing solution and there would remain no interferon to be isolated on the affinity chromatography column. Carter clearly and repeatedly describes propylene glycol as an *elution* solution, instead of a washing solution since propylene glycol elutes interferon with higher yield and stabilizes the purified interferon in an aqueous solution (column 1, lines 35-36, 40-42, column 2, 30-35, Claim 1, line 5-6).

The Examiner asserts that "[b]ecause a skilled artisan would know that a wash buffer comprising propylene glycol would stabilize the IFN-ß *immobilized on the affinity column*, the skilled artisan would be motivated to include a first washing step with a

solution comprising propylene glycol for the purpose of protein stabilization, followed by a second wash step comprising washing with the propylene glycol and 1M NaCl solutions taught by Carter and Revel as being useful for washing IFM-ß bound to affinity columns" (page 5, lines 9-13, OA 08/24/2009).

However, neither Carter nor Revel discloses a washing step comprising washing with the washing buffer solution B of pH 6.5-7.5 containing 10-30 wt% of propylene glycol and 1-2M NaCl, which allegedly corresponds to the second washing step comprising washing with the propylene glycol and 1M NaCl solutions referred to by the Examiner. Carter discloses 40% propylene glycol in 1.0M NaCl/PO4 buffer (E3) used as a washing buffer; however, this buffer does not correspond to the washing buffer solution B of the claimed invention. Further, a person of an ordinary skill in the art would not have used 50% propylene glycol disclosed at Example 1, 2nd paragraph of Carter as a first washing solution since Carter discloses 50% propylene glycol as a *elution* solution and thus, the person of ordinary skill in the art would have believed that using this solution as a washing solution would remove the immobilized interferon from the column.

As stated above, the washing is a process of removing *impurities* including adsorbed proteins *other than interferon* on the affinity chromatography column into the washing solution. Carter discloses that propylene glycol can stabilize interferon ***in an aqueous solution*** **or** ***eluted solution***, but does not disclose that propylene glycol can stabilize the IFN-immobilized ***on the affinity column***. The stability of interferon in an aqueous solution or eluted solution would not have provide a motivation to one skilled in the art to select propylene glycol as a washing buffer solution since the washing solution

will pass through the column together with the impurities and eventually be discarded.

The Examiner asserts that "[e]ven without the specific teachings of Carter regarding the suitability of propylene glycol from a toxicity and protein stabilization standpoint, a person of ordinary skill in the art would have the motivation to optimize the specific conditions for isolation/purification of IFN-β, including the percentage of propylene glycol, and the number of wash steps involved. MPEP 2144.05 states:

'[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation'" (page 5, 2nd and 3rd paragraphs, OA 10/16/2009).

However, the general conditions of the washing methods disclosed by Carter and Revel are so broad to encompass a very large number of possible distinct washing methods that are a combination of the number of washing steps and compositions of washing buffer solutions used in the washing steps. In fact, to derive the washing methods of the claimed invention from the cited prior art, one should consider *two parameters*, that is, the number of washing steps and composition of the washing solution used in each washing step.

Regarding the number of washing steps, Carter discloses only a single washing step and Revel does not disclose any washing step. Thus, none of Carter and Revel discloses the three washing steps using the three distinct washing buffer solutions A, B and C respectively. Therefore, there can be an infinite number of optimization ways to select three washing steps of the claimed invention from the cited prior art. Regarding the composition of each washing step, Carter only discloses washing with 40% propylene glycol in 1.0M NaCl/PO4 buffer (E3). Thus, none of Carter and Revel

discloses using the washing solutions A, B and C of the claimed invention in three washing steps. In this regard, there can be an infinite number of optimization ways to select the washing solutions A, B and C of the claimed invention, even though considering that the propylene glycol can stabilize interferon ***in an aqueous solution*** as disclosed in Carter.

In this regard, even if the number of washing steps were to be selected to be three from the disclosure of Carter and Revel, it would not have been obvious at the time the claimed invention was made to a person of ordinary skill in the art to derive the three washing steps of the claimed invention since *none of Carter and Revel discloses* ***even a single exact washing step of the claimed invention***.

MPEP 2144.05 states: "However, if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus." *Id. See also In re Baird*, 16 F.3d 380 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); MPEP § 2144.08.

Further, according MPEP 2144.05, only result-effective variables can be optimized. MPEP 2144.05 states: "A particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." *In re Antonie*, 559 F.2d 618 (CCPA 1977).

As stated above, none of the cited prior art recognizes that the purity of interferon is a function of washing steps. None of the cited prior art recognizes that the purity of interferon is a function of washing with a washing solution A, washing with a washing

solution B and washing with a washing solution C. Regarding the washing solution A, as stated above, Carter only discloses that propylene glycol can elute interferon with a higher yield; however it does not disclose that the purity of interferon can be increased by using propylene glycol as a washing solution. It should be noted that the purity of interferon can be increased by *selectively* removing impurities, for example, adsorbed proteins *other than the interferon* on the affinity column. However, Carter only discloses that propylene glycol can remove *interferon per se*, instead of adsorbed protein *other than the interferon,* from the affinity column. Regarding the washing solutions B and C, none of the cited prior art discloses the washing solutions B and C *per se*, let alone the purity of interferon can be increased by washing with a washing solution B and washing with a washing solution C. In this regard, Applicants respectfully submit that the parameter optimized was not recognized in the art to be a result-effective variable.

Therefore, it would not have been obvious at the time the claimed invention was made to a person of ordinary skill in the art to derive the three washing steps of the claimed invention since ***the parameter optimized was not recognized in the art to be a result-effective variable***.

Therefore, Applicants respectfully submit that no *prima facie* case of obviousness is established in this case.

Even if it were, unexpected results of the claimed invention as shown by the enclosed Declaration pursuant to 37 C.F.R. §1.132 by Mr. Jee Won Ahn, one of the inventors of the present application, are sufficient to rebut the allegedly established *prima facie* case of obviousness. Experimental Results contained in the Declaration clearly shows unexpected results of the claimed invention that the three separate

washing steps of the claimed invention can increase the purity of interferon in an affinity chromatography.

In the Experimental Results, in order to identify the effect of propylene glycol and ethylene glycol on the purity of interferon beta, interferon beta was isolated according to a method described in Example 1 of the present application and a method described in Example 1 of the present application except that propylene glycol is replaced with ethylene glycol, and the purity of interferon beta in the finally eluted solution was analyzed by using HPLC. Further, the purity of interferon beta in a solution obtained after each washing step and elution step was analyzed by using HPLC.

As can be shown in FIGS. 1 and 2 of the Experimental Results, interferon beta was eluted at 15 minutes with a single peak in FIG. 1, while there are several peaks around a main peak in FIG. 2, indicating that various impurities are eluted together with the interferon beta. Therefore, the Experimental Results clearly show that the propylene glycol can remarkably increase the purity of interferon beta in the affinity chromatography.

According to FIGS 3A-3D, the purity of the interferon beta remarkably increased by using the three washing steps: washing with washing solution A, washing with washing solution C, and washing with washing solution B. Particularly, according to FIG. 3A, washing with the washing solution A eluted impurities around 17 minutes and substantially did not elute interferon beta around 15 minutes (see also paragraph 0036 of the specification). This is an unexpected result considering that 50% propylene glycol is used as an elution solution in Carter (see Example 1, 2nd paragraph of Carter). According to FIG. 3B, washing with the washing solution C eluted impurities around 11

minutes and substantially did not elute interferon beta around 15 minutes. According to FIG. 3C, washing with washing solution B eluted various impurities around 15 minutes and a small amount of interferon beta around 15 minutes. According to FIG. 3D, eluting the column resulted in the elution of interferon beta with very high purity around 15 minutes.

As such, the Experimental Results clearly show the purity of the interferon beta after affinity chromatography remarkably increased by using the three washing steps: washing with washing solution A, washing with washing solution C, and washing with washing solution B. Accordingly, the claimed invention would not have been obvious at the time the claimed invention was made to a person of ordinary skill in the art from the teachings and suggestions of Carter, Revel and Viscomi, either alone or in combination.

In view of the above, Applicants respectfully request reconsideration and withdrawal of all the obviousness rejections.

Rejection under Obviousness-Type Double Patenting

The Patent Office has provisionally rejected claims 1-5 as being unpatentable over claims 1-5 of copending Application No. 10/581,602 under obviousness-type double patenting. In view of the provisional nature of this rejection, Applicants respectfully submit that we will address this rejection once allowable subject matter is identified in this case.

In light of the foregoing, Applicants submit that all outstanding rejections have been overcome, and the instant application is in condition for allowance. Thus,

Applicants respectfully request early allowance of the instant application. The Commissioner is hereby authorized to charge any fees or credit any overpayment to Deposit Account No. 02-2135.

Date: January 19, 2010 By: _____

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